New Developments in Biological Effects and Biophysical Models of Brachytherapy Sources

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Physicists have traditionally concentrated on accurate measurement of dose from brachytherapy sources. Recent heightened interest in brachytherapy has been precipitated, at least in part, by an increase in the number of both low dose rate (LDR) and high dose rate (HDR) implants and the advent of intravascular brachytherapy. Consequently, physical and biological factors which could ultimately influence clinical outcomes need to be systematically examined. Biological systems respond in a complex manner to energy deposition depending on a number of factors, e.g., intrinsic sensitivity, dose rate, fractionation and LET. Models which incorporate dose rate, and intrinsic radiosensitivity have been devised to compare fractionated HDR, pulsed dose rate (PDR) and LDR. LETs for brachytherapy sources vary with source energy and therefore have the potential of producing differentials in biological effects. Dose gradients at the source-tissue interface depend on source type and the atomic number of the source capsule. The biological response (RBE) near the source has a component that is dictated by the LET of the secondary low energy electrons.

The effect of dose rate for non permanent implants and insertions (~0.30 - 1.20 Gy/hr) has been previously modeled by NSDs and TDFs. More recently, repair half times and α/β's associated with the linear quadratic (LQ) model for tissue sensitivity have been used to generate equivalent dose and dose per fraction for early and late responding tissues irradiated at all dose rates. The biological equivalent dose (BED) or extrapolated response dose (ERD) is defined as: $BED = ERD = D[1 + GD/(\alpha/\beta)]$, where D (in Gy) is the total dose, G is a dose modifying function and α/β is the ratio of the linear to quadratic coefficients and are tissue type dependent. For tumors and early responding α/β is ~ 10/Gy while for late responding tissues it is generally assumed to be ~ 2-3/Gy. From the expression for BED with the appropriate G, dose equivalence can be derived between fractionated HDR, PDR, and LDR. For the special case applicable to continuous irradiation in which the overall time (T)>> repair half time ($t_{1/2}$), the above expression reduces to $D[1 + 2R/(\mu\alpha/\beta)]$, where R is the dose rate and $\mu = \ln 2/t_{1/2}$. For fractionated HDR the expression becomes $D[1 + d/(\alpha/\beta)]$, where d is the dose per fraction. (G = 1/N for fractionated HDR, where N = number of fractions)

Sources commonly used in brachytherapy vary in energy from 21 keV for Pd^{103} to 662 keV for Cs^{137}. The dose rate distributions about a given source vary with energy and type of encapsulation. Over and above variation in dose rate, there are biological effects which may be significant clinically. In general the biological effectiveness and LET increase with decreasing energy. For example, predictions from microdosimetry indicate that the RBE may be $\geq$ 2.0 for Pd^{103} or I^{125} photons compared to Cs^{137}. In vitro measurements using cell survival assays have qualitatively confirmed these predictions. These RBE differences have

seldom been used explicitly, but are often implicitly included in dose prescriptions of different brachytherapy sources. Because the variations in RBE may be particularly large foe secondary elections near metal/tissue interfaces, their impact may be of extreme importance for intravasular brachytherapy for which the exact biological target is yet to be identified.

Whether a brachytherapy source is a photon or β emitter, the majority of ionization in tissue is produced by electrons. The secondary electrons produced by the source capsule (or intravasular stent) near the metal/tissue interface have a spectrum of energies which is dependent on the materials' thickness and the atomic number, Z. For high Z materials the dose from the low energy electrons produced from the source capsule can be 10-20X that from the source photons. Low energy electrons have a very limited range but a higher LET. The LET can vary by a factor of 3 or more depending on the proportion of the dose deposited from track end electrons. The possibility, therefore, exists for a much higher RBE which acts as a multiplier to any increase in dose. The importance of higher RBE for secondary electrons and β particles in conventional brachytherapy is limited but may help to explain differences in dose response of intravascular irradiation.